AR201-13912B

24 June 2002

The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as related references in this document.

1.0 Substance Information

CAS Number: 111-49-9

Chemical Name: 1H-Azepine, hexahydro-

Structural Formula:

Other Names:
Azacycloheptane
1-Azacycloheptane
Azepine, hexahydro
Cyclohexamethylenimine
CP 18407
Cycloheptane, 1-aza
G 0
G 0 (amine)
Hexahydroazepine
Hexamethyleneimine
HMI
Homopiperidine
Perhydroazepine

Exposure Limits: 0.5 ppm (8- and12-hour TWA): DuPont Acceptable Exposure Limit (AEL)

2.0 Physical – Chemical Properties

2.1 Melting/Freezing Point

Value:	-37°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 574, John Wiley and Sons, Inc., New York.
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York.

2.2 Boiling Point

Value:	138°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lide, D. R. (ed.) (1998-1999). CRC Handbook of Chemistry and Physics, 79th ed., p. 3-16, CRC Press Inc., Boca Raton, FL.
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 574, John Wiley and Sons, Inc., New York.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:25-35.

2.3 Density

Value:	0.8799
Temperature:	20/4°C
Method:	No Data
GLP:	Unknown

Results:	No additional data.
Reference:	Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 574, John Wiley and Sons, Inc., New York.
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

DuPont Co. (n.d.). Unpublished Data.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

Lide, D. R. (ed.) (1998-1999). CRC Handbook of Chemistry and Physics, 79th ed., p. 3-16, CRC Press Inc., Boca Raton, FL.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:25-35.

2.4 Vapor Pressure

Value:	8.09 mm Hg
Temperature:	25°C
Decomposition:	No Data
Method:	Measured
GLP:	Unknown
Reference:	Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC (HSDB/562; NISC/EF-0010375).
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

Lyman, W. J. (1985). In Environmental Exposure From Chemicals, Vol. I, Neely, W. B. and G. E. Blau (eds.), p. 31, CRC Press, Boca Raton, FL (HSDB/562).

2.5 Partition Coefficient (log Kow)

Value:	1.7
Temperature:	No Data
Method:	Estimated
GLP:	Not Applicable
Reference:	Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/562).
Reliability:	Estimated value based on accepted model.

Additional References for Partition Coefficient (log Kow): None Found.

2.6 Water Solubility

Value:	3.19×10^4 mg/L
Temperature:	25°C
pH/pKa:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Yalkowsky, S. H. and R. M. Dannenfelser (1992). The AQUASOL Database of Aqueous Solubility, 5th ed., University of Arizona, College of Pharmacy, Tucson, AZ (HSDB/562).
Reliability:	Not assignable because limited study information was available.

Additional References for Water Solubility:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

2.7 Flash Point

Value:	99°F (37.2°C)
Method:	Open cup
GLP:	No
Reference:	U. S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U. S. Government Printing Office, Washington, DC (HSDB/562).
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (1958). Unpublished Data.

DuPont Company (n.d.). Unpublished Data.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1939, John Wiley and Sons, Inc., New York.

2.8 Flammability

Results:	1.6-2.3% in air
Method:	No Data
GLP:	No
Reference:	U. S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U. S. Government Printing Office, Washington, DC (HSDB/562).
Reliability:	Not assignable because limited study information was available.

Additional References for Flammability:

DuPont Company (2000). Material Safety Data Sheet No. FE000029 (March 13).

DuPont Company (n.d.). Unpublished Data.

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	No Data
Temperature:	No Data
Direct Photolysis:	No Data
Indirect Photolysis:	No Data
Breakdown Products:	No Data
Method:	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman, 1988), hexamethyleneimine, which has a vapor pressure of 8.09 mm Hg at 25°C (Daubert and Danner, 1989), is expected to exist solely as a vapor in the ambient atmosphere. Vapor-phase hexamethyleneimine is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals (SRC, n.d.). The half-life for

this reaction in air is estimated to be 4.3 hours (SRC, n.d.), calculated from its rate constant of $9.0x10^{-11}$ cm^3/molecule-sec at 25°C determined using a structure estimation method (Meylan and Howard, 1993).

GLP: Not Applicable

Reference: Bidleman, T. F. (1988). Environ. Sci. Technol., 22:361-367 (HSDB/562).

Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC.

Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-2299 (HSDB/562).

SRC (Syracuse Research Corporation) (n.d.) (HSDB/562).

Reliability: Estimated value based on accepted model.

Additional References for Photodegradation: None Found.

3.2 Stability in Water

Concentration: No Data

Half-life: No Data

% Hydrolyzed: No Data

Method: Based on a classification scheme (Swann et al., 1983), an estimated Koc value of 170 (SRC, n.d.) indicates that hexamethyleneimine is expected to adsorb to some degree to suspended solids and sediment in water (SRC, n.d.). Some volatilization from water surfaces is expected for the free amine (Lyman et al., 1990) based upon a Henry's Law constant of $6.1x10^{-6}$ atm-m^3/mole (Cabani et al., 1971). However, a pKa of 11.07 (Perrin, 1965) indicates hexamethyleneimine will exist almost entirely in the protonated form in aqueous environments, and is not expected to volatilize from water surfaces.

GLP: Not Applicable

Reference: Swann, R. L. et al. (1983). Res. Rev., 85:17-28 (HSDB/562).

Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 4-9, 15-1 to 15-29, American Chemical Society, Washington, DC (HSDB/562).

Cabani, S. et al. (1971). Trans Faraday Soc., 67:1933-1942 (HSDB/562).

Perrin, D. D. (1965). Dissociation Constants of Organic Bases in Aqueous Solution, IUPAC Chem. Data Ser., p. 101, Butterworth, London (HSDB/562).

SRC (Syracuse Research Corporation) (n.d.) (HSDB/562).

Reliability: Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity)

Media:	Air, Water, Soil, Sediments	
Distributions:	Air:	0.514%
	Water:	46.7 %
	Soil:	52.7%
	Sediment:	0.11%
Adsorption Coefficient:	Not Applicable	
Desorption:	Not Applicable	
Volatility:	Not Applicable	

Method: Calculated according to Mackay, Level III, Syracuse Research Corporation Epiwin Version 3.05. Emissions (1000 kg/hr) to air, water, and soil compartments using EPA Model defaults.

Data Used:
Molecular Weight: 99.18
Henry's Law Constant: 6.1×10^{-6} atm-m^3/mole (Cabani et al., 1971)
Vapor Pressure: 8.09 mm Hg (Daubert and Danner, 1989)
Log Kow: 1.7 (Meylan and Howard, 1995)
Soil Koc: 20.5 (calc by mmodel)

GLP: Not Applicable

Reference: Cabani, S. et al. (1971). Trans Faraday Soc., 67:1933-1942 (HSDB/562).

Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC.

Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/562).

Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming

approach was developed by Dr. Donald Mackay and co-workers which is detailed in:

Mackay, D. (1991). Multimedia Environmental Models; The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.

Reliability: Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value: Hexamethyleneimine served as the sole carbon and nitrogen source in aerobic sludge cultures. The increase in cellular proteins indicated approximately a 27% conversion rate over a 1-week period with an average protein yield of 73 μg/L.

Breakdown Products: No Data

Method: Sewage sludge cultures were acclimated to test substances (0.05%) which served as the sole source of C, N, and energy in mineral solutions. At weekly intervals, cultures were transferred to fresh medium of the same composition. One week after the 3rd transfer, cultures were assayed for cell protein yield. An increase in cellular protein of at least 20 μg/L was considered positive for biodegradability with a maximum protein yield of approximately 175 μg/L.

GLP: Not Applicable

Reference: Rothkopf, S. S. and R. J. Bartha (1984). J. Amer. Oil Chem. Soc., 61:977-980.

Reliability: Medium because a suboptimal study design was used.

Additional Reference for Biodegradation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Jones, H. R. (1971). Environmental Control in the Organic and Petrochemical Industries, Noyes Data Corporation (cited in Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 732, Van Nostrand Reinhold Company, New York).

3.5 Bioconcentration

Value:	BCF = 3.9. This value suggests that the potential for bioconcentration in aquatic organisms is low.
Method:	Estimated according to a classification scheme (Franke et al., 1994), using an estimated log Kow of 1.7 (Meylan and Howard, 1995).
GLP:	Not Applicable
Reference:	Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/562). Franke, C. et al. (1994). Chemosphere, 29:1501-1514 (HSDB/562).
Reliability:	Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**96-hour LC_{50}**
Species:	Fathead minnow
Value:	36.5 mg/L
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Hexamethyleneimine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates

Type:	**48-hour EC_{50}**
Species:	*Daphnia magna*
Value:	2.6 mg/L
Method:	Modeled
GLP:	Not Applicable

Test Substance:	Hexamethyleneimine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3 Acute Toxicity to Aquatic Plants

Type:	**96-hour EC_{50}**
Species:	Green algae
Value:	4.4 mg/L
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Hexamethyleneimine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral ALD**
Species/Strain:	Male rats/ChR-CD
Value:	1000 mg/kg
Method:	The test substance, as an aqueous solution, was administered by intragastric intubation to male rats in single doses of either 300, 450, 670, 1000, 1500, 2250, or 3400 mg/kg. Survivors were sacrificed after 14 days.
GLP:	No
Test Substance:	Hexamethyleneimine, purity 98.18%
Results:	Mortality occurred at ≥ 1000 mg/kg from 1 ¾ to 2 ¼ hours

	after dosing. Clinical signs observed at lethal doses included belly-to-cage posture, half-closed eyes, pallor, tremors, and convulsions. Clinical signs observed at non-lethal doses included belly-to-cage posture, half-closed eyes, and pallor on the day of dosing (≥ 450 mg/kg); bloody mouth-nose area for 1-2 days after dosing (≥ 450 mg/kg); weight loss for 2-5 days (300 and 670 mg/kg); and diarrhea and continuous weight loss (450 mg/kg).
Reference:	DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 328-74.
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	**Oral LD_{50}**
Species/Strain:	Rats/CRCD
Value:	50-500 mg/kg
Method:	Male rats (6/dose level) were orally intubated with either 0, 50, or 500 mg/kg hexamethyleneimine. The rats were fasted overnight, prior to administration of the test material. Body weights and clinical signs were recorded, and all rats were necropsied.
GLP:	Yes
Test Substance:	Hexamethyleneimine (neat material), purity not specified
Results:	Mortality was 0/6, 0/6, and 6/6 at 0, 50, and 500 mg/kg, respectively. Mortality occurred on the day of dosing. Clinical signs of toxicity in the control rats, observed on the day of dosing, included brown-stained anogenital area (2/6) and diarrhea (1/6). No clinical signs of toxicity were observed in rats dosed with 50 mg/kg. Clinical signs of toxicity observed at 500 mg/kg included passiveness (6/6), prostration (2/6), ataxia (6/6), tremors (3/6), convulsions (2/6), salivation (6/6), abdominal breathing (3/6), brown-stained anogenital area (1/6), ptosis (6/6), and cyanosis (2/6). No macroscopic changes were observed in rats dosed at 0 or 50 mg/kg. Necropsy observations noted at 500 mg/kg included red-stained eyes (2/6), wet matted fur on the muzzle (6/6), whitened lungs (5/6), severely reddened stomach mucosa and intestines (6/6), and red fluid-filled stomach and intestines (6/6).
Reference:	Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).
Reliability:	Medium because a suboptimal study design was used.
Type:	**Oral LD_{50}**
Species/Strain:	Male and female rats/Sprague Dawley
Value:	9.6 mg/kg (lower and upper limits, 8.0-11.4 mg/kg)

Method:	Male and female rats (5 rats/dose level) were orally intubated with single doses of 3.98, 6.31, 10.0, or 15.8 mg/kg of the test substance. Observations were made for toxic signs. Surviving rats were sacrificed 14 days after dosing, and the viscera of the test rats were examined macroscopically. The LD_{50} was calculated according to the method of E. J. de Beer.
GLP:	No
Test Substance:	Hexamethyleneimine (HMI Refined), purity not specified
Results:	Mortality was 0/5, 2/5, 3/5, and 5/5 at 3.98, 6.31, 10.0, and 15.8 mg/kg, respectively. Survival time was 3-8 days. Toxic signs included reduced appetite and activity (5-10 days in survivors), gradually increasing weakness, collapse, and death. At autopsy there was lung hyperemia, slight liver discoloration, and acute gastrointestinal inflammation. Macroscopic examination revealed slight liver discoloration in some cases.
Reference:	Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (n.d.). Unpublished Data.

DuPont Co. (1958). Unpublished Data, Haskell Laboratory Report No. 65-58.

DuPont Co. (1958). Unpublished Data.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 330-74.

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2)

(cited in TSCA fiche OTS0534827).

Izmerov, N. F. et al (1982). Toxicometric Parameters of Industrial Toxic Chemical Under Single Exposure, Centre of International Projects, GKNT, Moscow.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:25-35 (CA71:47804w).

Zaeva, G. N. et al. (1974). Gig. Tr. Prof. Zabol., (2):29-32 (HEEP/75/02464; also cited in Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., John Wiley & Sons, Inc., New York).

Bazarova, L. A. and N. I. Osipenko (1967). Toksikol. Novykh Prom. Khim. Veshchestv, 9:91-101 (CA70:27261t).

Type:	**Inhalation ALC**
Species/Strain:	Male rats/ChR-CD
Exposure Time:	4 hours
Value:	2.45 mg/L (605 ppm)
Method:	Male rats were exposed to hexamethyleneimine at concentrations of 0.52, 1.32, 1.95, 2.45, 2.77, or 3.12 mg/L for 4 hours. The test substance was delivered at a constant rate into a round bottom flask heated to approximately 96°C. Air metered into the flask carried the test vapors into a 20-liter exposure chamber usually containing 6 male rats (the 0.52 mg/L group contained 10 rats) weighing between 200 and 300 grams each. Exposures were for 4 hours, during which samples of the chamber atmosphere were analyzed for hexamethyleneimine by gas chromatography. The test rats were observed and weight records maintained for 14 days post-exposure, unless sacrificed for pathologic examination. Males exposed to 1.32 mg/L (2 at 1, 4, and 7 days post-exposure), 2.45 mg/L (2 at 14 days post-exposure), and 2.77 mg/L (2 upon death) were examined for pathologic alterations. At necropsy, 20 tissues from each rat were examined grossly and preserved in Bouin's fixative. The tissues were embedded in paraffin, sectioned, stained, and given a histopathologic examination.
GLP:	No
Test Substance:	Hexamethyleneimine, purity 98%
Results:	Mortality was 0/10, 0/6, 0/6, 1/6, 3/6, and 6/6 at 0.52, 1.32, 1.95, 2.45, 2.77, and 3.12 mg/L, respectively. Clinical signs included chewing and grooming motions (0.52, 1.32, and

1.95 mg/L), labored breathing (1.32, 1.95, 2.45, and 2.77 mg/L), gasping (2.45 mg/L), redness around the eyes and nose (2.45 mg/L), fasciculations (2.77 and 3.12 mg/L), and convulsions (2.77 mg/L). Post-exposure observations included weight loss (≤ 2.77 mg/L), lung congestion (1.95, 2.45, and 2.77 mg/L), corneal opacity (1.95, 2.45, and 2.77 mg/L), nasal discharge (2.45 and 2.77 mg/L), and lacrimation (2.77 mg/L).

A mild total body cyanosis was observed in both rats at 2.77 mg/L that died during exposure, while subpleural white plaques, red focal spots, and congestion of the lungs were similar to the gross observations made in all test rats exposed to 1.32 and 2.45 mg/L. Organs showing possible test substance-related effects included the lungs, trachea, and eyes. However, the histopathologic effects were difficult to interpret in the absence of a concurrent control group.

Reference: DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 495-74 (also cited in TSCA fiche OTS0546547).

Reliability: High because a scientifically defensible or guideline method was used. (Histologic examination is not generally part of this test design, hence no control rats were used.)

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1958). Unpublished Data, Haskell Laboratory Report No. 65-58.

Izmerov, N F. et al (1982). Toxicometric Parameters of Industrial Toxic Chemical Under Single Exposure, Centre of International Projects, GKNT, Moscow.

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of: HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Zaeva, G. N. et al. (1968). Aktual. Vop. Gig. Tr. Prof. Patol., Mater. Konf., 1st, Meeting Date 1967, pp. 51-53 (CA72:53301).

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:25-35 (CA71:47804w).

Bazarova, L. A. and N. I. Osipenko (1967). Toksikol. Novykh Prom. Khim. Veshchestv, 9:91-101 (CA70:27261).

Data from this additional source were not summarized because the study design was not adequate. The focus of the study was to determine if the test substance was a Class B poison.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 329-74.

Data from this additional source were not summarized because insufficient study information was available.

U. S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U. S. Government Printing Office, Washington, DC (HSDB/562).

Type:	**Dermal MLD (Minimal Lethal Dose)**
Species/Strain:	Male and female rabbits/New Zealand White
Value:	1260-2000 mg/kg
Exposure Time:	24 hours
Method:	The undiluted test substance was applied in increasing doses at increments of various fractional log intervals to the closely clipped, intact skin of male and female rabbits. The treated areas were covered with plastic strips, and the rabbits were held in wooden stocks for periods up to 24 hours. Observations were made for toxic signs, and the viscera of the test rabbits were examined macroscopically.
GLP:	No
Test Substance:	Hexamethyleneimine (HMI refined), purity not specified
Results:	The minimal lethal dose for male and female rabbits was 1260-2000 mg/kg. The compound was classed as mildly toxic by skin absorption in male and female rabbits.
Reference:	Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).
Reliability:	Medium because a suboptimal study design was used.

Type:	**Dermal LD_{50}**
Species/Strain:	Rabbits/New Zealand White
Exposure Time:	24-hours
Method:	Hexamethyleneimine (200 mg/kg neat material) was held under an impervious cuff in a continuous 24-hour contact with the intact skin of rabbits, from which the hair had been closely clipped. After the 24-hour exposure, the cuffs were removed and the application sites were wiped gently to remove the test substance. Body weights, clinical signs, and skin reaction were recorded, and necropsy was performed on all rabbits after 14 days.
GLP:	Unknown
Test Substance:	Hexamethyleneimine (neat material), purity not specified
Results:	One rabbit died 8-14 days after dosing. Severe erythema with blanching, and severe edema with pocketing were observed on Day 1. The skin irritation score was not evaluated after Day 1, since the pH of the test substance was found to be greater than 12. This test substance was classified as corrosive according to OECD guidelines. Only 1 rabbit exhibited clinical signs of toxicity, which included passiveness, ataxia, abdominal breathing, scant droppings, brown-stained anogenital area, mucous on dropsheet, and distended abdomen. The gross necropsy signs and cause of death were attributed to mucoid enteropathy, and were judged not to be related to treatment with the test-substance. No other clinical signs of toxicity were observed. Eschar at the application site was observed in all surviving rabbits at necropsy. Based on this rangefinding LD_{50}, the test material is not more than moderately toxic to male rabbits by a single dermal application.
Reference:	Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Dermal Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number

Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Data from these additional sources were not summarized because insufficient study information was available.

Izmerov, N. F. et al (1982). Toxicometric Parameters of Industrial Toxic Chemical Under Single Exposure, Centre of International Projects, GKNT, Moscow.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:5-9 (CA71:47803v).

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:25-35.

Type: **Dermal Irritation**

Species/Strain: Rabbits/New Zealand White

Method: Young New Zealand White rabbits were used in the evaluation of the primary skin irritating properties of the test material. The test procedure was modeled after DOT (Department of Transportation) test conducted in accordance with 19 CFR, Chapter I, Sec. 173.40, as amended in Federal Register, Vol. 37, No. 57, March 23, 1972. Prior to the application of the test substance, the hair was clipped from the back and flanks of each rabbit. Two test sites located lateral to the midline of the back, approximately 10 cm apart were selected. One of the 2 sites was abraded by making 4 epidermal incisions, 2 perpendicular to the other 2, while the other test site remained intact. Exactly 0.5 mL of undiluted test substance was applied to each of the test sites on each rabbit. The test sites were immediately covered with gauze patches that were placed directly over the test sites and secured with tape. The trunk of each rabbit was then wrapped with plastic sheeting. The wrap held the patches in position and retarded evaporation of the test substance during the 4-hour exposure period. At the end of 4 hours, the plastic wrappings and patches were removed. The intact and abraded test sites were examined and scored separately for erythema and edema on a graded scale of 0 to 4. After 24 and 72 hours, the sites were again scored. In evaluating the average irritation present, the mean scores for erythema and edema of the intact test sites after 4, 24, and 72 hours were added. Similarly, the mean scores for erythema and

	edema of the abraded test sites after 4, 24, and 72 hours were added. These 2 values were totaled and divided by 6 to obtain the mean primary irritation score. The test substance was classified as corrosive if, when tested on intact rabbit skin, the structure of the tissue at the site of contact was destroyed or changed irreversibly after an exposure period of 4 hours or less.
GLP:	No
Test Substance:	Hexamethyleneimine, purity not specified
Results:	Hexamethyleneimine was classified as corrosive, with a mean primary irritation score of 8.0/8.0 (maximum primary irritation score of 8).
Reference:	The Celanese Chemical Co. (1972). Bio-Test IBT No. A1854 (cited in TSCA fiche OTS0520783, OTS0206028, OTS0534489).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 179-74.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 180-74.

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:25-35 (CA71:47804w).

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

Data from these additional sources were not summarized because insufficient study information was available.

Latypova, R. M. and F. G. Murzakaev (1976). Gig. Tr. Okhr. Zdorov'ya Rab. Neft. Neftekhim. Prom-sti., 9:129-131 (CA90:17319; also cited in HSDB/562).

Bazarova, L. A. and N. I. Osipenko (1967). Toksikol. Novykh Prom. Khim. Veshchestv, 9:91-101 (CA70:27261).

Type:	**Dermal Sensitization (Mouse Ear Swelling Test – MEST)**
Species/Strain:	Female mice/CF-1
Method:	Female mice were allowed to acclimate for 1 week after arrival in the laboratory, then were screened to remove any from testing that had ears that appeared red or swollen. Female mice, 6-8 weeks old, were shaved and tape stripped at the start of the study. As a standard part of this design, 2 intradermal injections, totaling 0.05 mL, of Freund's complete adjuvant emulsion (FCA) were performed into the stomach induction site of unanesthetized mice prior to the 1st induction application. All mice were then topically dosed with 100 µL of the test substance in solvent (acetone) or solvent alone (control) applied to the center of the shaved region. The application was allowed to dry before the mouse was returned to its cage. Tape stripping and topical application of the appropriate solution to the stomach were repeated for 3 additional consecutive days. Seven days after the final topical application to the stomach, 20 µL of the test substance in solution was applied to the left ear of each mouse (test and control), and 20 µL of the solvent was applied to the right ear. At 24 and 48 hours after this challenge, mice were lightly anesthetized and the thickness of both ears was measured. As an additional guard against false positives, ear thickness may also have been measured on the day before challenge to protect against the small random chance of a naturally occurring "difference" in test or control groups. Hexamethyleneimine (1% in propylene glycol) was also evaluated by a patching induction method. To evaluate the effect of occlusive patching on the induction of a sensitization response, mice were shaved, tape stripped, injected intradermally with FCA, and patched. The test

	substance was applied to a small cotton swatch, which was then wrapped with tape. Only the cotton swatch was utilized. Unanethetized mice were wrapped for 24 hours every other day for 6 days, being tape stripped prior to each application.
GLP:	Unknown
Test Substance:	Hexamethyleneimine, purity ≥ 98%
Results:	Hexamethyleneimine produced sensitization reactions in 40% of the mice using the mouse ear swelling test (MEST), but produced 0% response in the patching induction method.
Reference:	Gad, S. C. et al. (1986). Toxicol. Appl. Pharmacol., 84:93-114.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Dermal Sensitization: None Found.

Type:	**Eye Irritation**
Species/Strain:	Male rabbits/New Zealand White
Method:	One day prior to dosing, the eyes of 6 male New Zealand White rabbits were examined grossly. Following gross examination fluorescein solution was placed onto the eye, the eye was flushed with water, and reexamined to determine any pre-existing ocular abnormalities. On the day of dosing, 0.1 mL of hexamethyleneimine (neat material) was applied to the corneal surface of the rabbits. The eyelids were held open momentarily after dosing and then released gently to allow the rabbit to blink freely. Approximately 10% of the applied test substance was blinked or fell from the treated eye, but the cornea and surrounding area were observed to be covered with the test substance. The treated eyes of 3 rabbits were irrigated with water for approximately 60 seconds beginning 20-30 seconds after dosing. The eyes of the other 3 rabbits remained unwashed. The treated eyes were scored according to the Draize procedure, and sodium fluorescein was used as an adjunct to gross examination of the eyes.
GLP:	Unknown
Test Substance:	Hexamethyleneimine (neat material), purity not specified
Results:	At 24 hours, the mean value for the cornea (calculated from 3 rabbits, unwashed eyes) was 80.0, and the conjunctive mean value was 19.0. All 6 rabbits exhibited blanching of the nictitating membrane and eschar on the eyelids. In addition, 3 of the rabbits had blanching of the conjunctiva, while the conjunctiva of the remaining rabbits was not visible due to the eschar on the eyelids. The iris of all rabbits was unscorable due to severity of the opacity. The

	study was terminated after the 24-hour observation and the rabbits were killed.
Reference:	Rohm and Haas (1985). Report No. 85R 0051 (cited in TSCA fiche OTS0540608).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Eye Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Monsanto Chemical Co. (1973). Letter from P. L. Wright to N. J. Hunt (April 4) (also cited in OTS0571679).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-31, "Toxicological Investigation of CP 18407 – HMI Refined" (April 2) (cited in TSCA fiche OTS0539976).

Monsanto Chemical Co. (1972). Younger Laboratories, Inc. Project Number Y-72-114, "Toxicological Investigation of HMI Binary Solution" (June 2) (cited in TSCA fiche OTS0534842).

Monsanto Chemical Co. (1973). Younger Laboratories, Inc. Project Number Y-73-33, "Toxicological Investigation of CP 61337 – HMI Azeotrope" (April 2) (cited in TSCA fiche OTS0534827).

5.2 Repeated Dose Toxicity

Type:	**2-Week Oral**
Species/Strain:	Rats/CFN
Sex/Number:	Male/6 per dose level
Exposure Period:	2 weeks
Frequency of Treatment:	5 times/week
Exposure Levels:	0 (control), 90 mg/kg
Method:	The test substance was administered to rats (6/level) as a 1% aqueous solution 5 times/week for 2 weeks. Three rats were sacrificed 4 hours after the 10^{th} treatment, and 3 rats were sacrificed 10 days after the 10^{th} treatment. Gross pathology included 13 tissues/organs, and microscopic examination included 11 tissues/organs. Additionally, 7 organs/tissues were weighed.
GLP:	No
Test Substance:	Hexamethyleneimine, purity not specified

Results:	No mortality was observed. No clinical signs of toxicity, other than some temporary discomfort at dosing was observed in the rats treated with the test substance. No evidence of pathological change attributable to treatment was observed.
Reference:	DuPont Co. (1958). Unpublished Data, Haskell Laboratory Report No. 65-58. DuPont Co. (1958). Unpublished Data.
Reliability:	Low because an inappropriate method or study design was used.

Additional Reference for Repeated Dose Toxicity:

Data from this additional source were not summarized because insufficient study information was available.

Zaeva, G. N. et al. (1968). Toksikol. Nov. Prom.Khim. Veschestv, 10:25-35 (CA71:47804w).

5.3 Developmental Toxicity: No Data.

5.4 Reproductive Toxicity

Species/Strain:	Rats/Sprague-Dawley
Sex/Number:	Male/Number not specified
Route of Administration:	*Hormone analysis:* Intraperitoneal injection *Sperm and testis morphology:* Subcutaneous implant
Exposure Period:	*Hormone analysis:* Single dose *Sperm and testis morphology:* 7 days
Frequency of Treatment:	*Hormone analysis:* Single dose *Sperm and testis morphology:* Daily
Exposure Levels:	*Hormone analysis:* 0, 10 mg/kg *Sperm and testis morphology:* 10 mg/kg
Method:	*Hormone analysis:* Male rats were administered a single dose of hexamethyleneimine in corn oil or corn oil alone. Rats were killed at 2, 6, or 24 hours. Blood was collected into lithium heparin syringes and centrifuged (1000 g for 15 minutes at 4ºC) to obtain plasma. Testes were removed and weighed, the capsules were pierced at the caudal pole, and the interstitial fluid was collected by draining over 18 hours at 4ºC. Interstitial fluid from paired testes was combined. Plasma and interstitial fluid were used immediately for testosterone determination. For hormone analyses conducted after collection, samples were stored overnight at -20ºC or for longer periods at -70ºC.

Sperm and testis morphology: Male rats were surgically implanted subcutaneously with osmotic mini-pumps charged to deliver 10 mg/kg hexamethyleneimine, dissolved in PEG200, daily for 7 days. Rats were killed at 28 days after implantation, and the testes and cauda epididymis were removed. The distal cauda was chopped into culture medium and incubated for 15 minutes at 37ºC, with gentle swirling to evenly distribute the sperm. This sperm suspension was diluted into phosphate-buffered saline and cooled over ice to kill the sperm prior to analysis. Testes were preserved in Bouin's fixative, embedded in wax, and processed through to hematoxylin- and eosin-stained sections (5 µm) for examination by light microscopy.

Samples of the sperm preparation were smeared onto microscope slides, allowed to dry, then fixed in acetone, and stained with a solution of 1% acetic acid containing trypan blue/naphthol yellow/eosin Y. The excess stain was removed by draining and the slides were rinsed twice in 1% acetic acid. After air drying, the slides were rinsed in xylene and cover slips were mounted. Each slide was scanned (40x magnification) and a minimum of 200 sperm were scored for tail (including mid-piece) and head abnormalities.

GLP: Unknown

Test Substance: Hexamethyleneimine, purity not specified

Results: The effect of hexamethyleneimine on testosterone biosynthesis was studied at concentrations that did not cause apparent systemic toxicity. No effects upon plasma or interstitial fluid concentrations were demonstrated with hexamethyleneimine at 10 mg/kg.

Administration of hexamethyleneimine at 10 mg/kg/day over a 7-day period from a subcutaneously implanted osmotic mini-pump failed to show any morphological changes in the testes. Hexamethyleneimine did not induce any abnormal changes in epididymal sperm morphology.

Reference: Ellis, M. K. et al. (1998). Toxicol. Appl. Pharmacol., 151:22-23.

Reliability: Medium because a suboptimal study design was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity

Type:	***In vitro* Bacterial Reverse Mutation Test**
Tester Strains:	*Salmonella typhimurium* TA97a, TA98, TA100, TA1535 *Escherichia coli* WP2 *uvr*A (pKM101)
Exogenous Metabolic Activation:	Aroclor®-induced rat liver S-9
Exposure Concentrations:	0, 10, 50, 100, 500, 1000, 2500, 5000 µg/plate
Method:	The study consisted of a single trial that assessed test substance mutagenicity. Three replicates were plated for each tester strain in the presence and absence of the S-9 exogenous metabolic activation system at each concentration. Positive and negative controls were included for each strain and condition. The negative control was sterile water, and the positive controls included 2-nitrofluorene, N-ethyl-N-nitro-N-nitroguanidine, sodium azide, ICR 191 acridine mutagen, 9,10-dimethyl-1,2-benzanthracene, and 2-aminoanthracene. Treatments in the presence of the exogenous metabolic activation system were conducted by adding 0.1 mL of negative or positive control or test substance solution, 0.5 mL of S-9 metabolic activation system, and 0.1 mL of an overnight culture containing approximately $1x10^8$ bacteria to approximately 2 mL of top agar. These components were briefly mixed and poured onto a minimal glucose agar plate. Treatments in the absence of the exogenous S-9 metabolic activation system were the same as those in the presence of the exogenous metabolic activation system with the exception that 0.5 mL of sterile buffer was used as a replacement for the volume of the activation system. After pouring onto the surface of minimal glucose agar plates, the top agar was allowed time to solidify, and the individually labeled plates were inverted and incubated at 37°C for approximately 48 hours. Plates were refrigerated at approximately 4°C prior to evaluation and counting of revertant colonies. Bacterial background lawns were evaluated for evidence of test substance toxicity and precipitation. Evidence of toxicity was scored relative to the concurrent negative control plates and recorded with the mean revertant count for the strain, condition, and concentration. Revertant colonies for a given tester strain and condition were counted by an automated colony counter unless the plate exhibited

	excessive toxicity. A test substance was classified as positive (i.e., mutagenic) if the mean number of revertants in any strain at any test substance concentration was at least 2 times greater than the mean of the concurrent vehicle control and there was a concentration-related increase in the mean revertants per plate in that same strain. A test substance was classified as negative (i.e., not mutagenic) if there were no test substance concentrations with a mean number of revertants that were at least 2 times greater than the mean of concurrent vehicle control, or there was no concentration-related increase in the mean revertants per plate in that same strain.
GLP:	Yes
Test Substance:	Hexamethyleneimine, purity 99.5%
Results:	Negative
Remarks:	No precipitate was observed at any concentration in any of the *Salmonella* strains or in the *Escherichia coli* strain. Toxicity was observed through the reduction of the microcolony background lawns of all strains. This was observed in all strains at concentrations ≥1000 μg/plate (non-activated test system), and at concentrations ≥2500 μg/plate (activated test system) in all strains except TA1535, where toxicity was observed only at the top dose of 5000 μg/plate. In addition, a concentration-related reduction in the mean number of revertant colonies per plate were observed in some strains. No test substance concentration reached a mean number of revertants that was 2 times greater than the mean of the concurrent vehicle control, and there was no concentration-related increase in the mean revertants per plate in any strain. The mean positive control value exhibited greater than a 3-fold increase over the respective negative control value for each tester strain.
Reference:	DuPont Co. (1999). Unpublished Data, Haskell Laboratory Report No. DuPont-2754.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Test: None Found.

Type: ***In vitro*** **Clastogenicity Studies:** No Data.

Type: ***In vivo*** **Genetic Toxicity Studies:** No Data.